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| (21) International Application Number: PCT/EP98/07650 (22) International Filing Date: 27 November 1998 (27.11.98) (30) Priority Data: 08/994,284 19 December 1997 (19.12.97) US 09/187,459 5 November 1998 (05.11.98) US (71) Applicant: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE). | | (72) Inventors: ARNAIZ, Damian, O.; 103 Bedford, Hercules, CA 94547 (US). CHOU, Yuo-Ling; 1068 Miller Drive, Lafayette, CA 94549 (US). KARANJAWALA, Rushad, E.; 172 Bonaire Avenue, Hercules, CA 94547 (US). KOCHANNY, Monica, J.; 193 Irwin Street, San Rafael, CA 94901 (US). LEE, Wheeseong; 933 Hough Avenue #10, Lafayette, CA 94549 (US). LIANG, Amy, Mei; 5572 Cerro Norte, Richmond, CA 94803 (US). MORRISSEY, Michael, M.; 129 Alta Vista, Danville, CA 94506 (US). PHILLIPS, Gary, B.; 3043 Shetland Drive, Pleasant Hill, CA 94523 (US). SACCHI, Karna, Lyn; 202 Clipper Street #1, San Francisco, CA 94114 (US). SAKATA, Stephen, T.; 1411 Palo Verde Road, Irvine, CA 92612 (US). SHAW, Kenneth, J.; 16 Oakmont Court, San Rafael, CA 94901 (US). SNIDER, R., Michael; 1031 Lorraine Drive, Napa, CA 94558 (US). WU, Shung, C.; 7121 Foxtail Court, Lawrenceville, NJ 08648 (US). YE, Bin; Apartment 3022, 3400 Richmond Parkway, Richmond, CA 94806 (US). ZHAO, Zuchun; 5368 Cerro Sur, El Sobrante, CA 94803 (US). GRIEDEL, Brian, D.; 526 Liberty Street, El Cerrito, CA 94530 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. With amended claims. Date of publication of the amended claims: 10 September 1999 (10.09.99) | |
| (54) Title: ORTHO-ANTHRANILAMIDE DERIVATIVES AS ANTI-COAGULANTS | | | |
| (57) Abstract This invention is directed to compounds of formula (III) wherein B, C, D, E, R ¹ , R ² and R ³ are disclosed herein. These compounds are disclosed as being useful as anti-coagulants. | | | |
| <div style="text-align: right;">(III)</div> | | | |

AMENDED CLAIMS

[received by the International Bureau on 26 July 1999 (26.07.99);
Original claims 68 and 69 amended; remaining claims unchanged (8 pages)]

$-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ or $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$, or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ and $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$); or

both R^{16} 's together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$, $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$, $-\text{C}(\text{O})\text{R}^5$, $-\text{C}(\text{O})-(\text{R}^8-\text{O})_t\text{R}^5$ (where *t* is 1 to 6), and $-(\text{R}^8-\text{O})_t\text{R}^5$ (where *t* is 1 to 6);

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-\text{OR}^5$, $-\text{R}^8-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$, or $-\text{R}^8-\text{C}(\text{O})-\text{N}(\text{R}^5)\text{R}^6$;

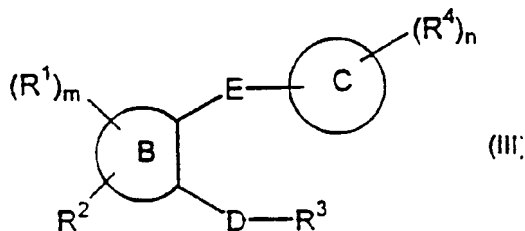
R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, $-\text{C}(\text{O})\text{OR}^5$, or $-\text{NO}_2$; and

each R^{19} is cycloalkyl, haloalkyl, $-\text{R}^8-\text{OR}^5$, $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$, $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$, $-\text{R}^8-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$,

heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ or $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ and $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

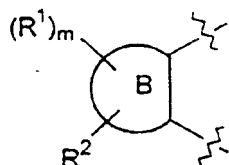
68. Use of a therapeutically effective amount of a compound of formula (III):



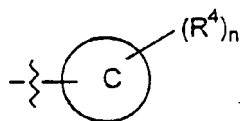
wherein

m is 1 to 3;

n is 1 to 5;



is an aryl or a heterocyclic ring substituted by R^2 and one or more R^1 groups;



is an aryl or a heterocyclic ring substituted by one or more R^4 groups;

D and E are independently a linker selected from the group consisting of $-N(R^5)-C(X)-$:

$-R^8-N(R^5)-C(X)-$; $-N(R^5)-C(X)-R^8-$; $-R^8-N(R^5)-C(X)-R^8-$; $-N(R^5)-S(O)_p-$; $-R^8-N(R^5)-S(O)_p-$;

$-N(R^5)-S(O)_p-R^8-$; and $-R^8-N(R^5)-S(O)_p-R^8-$ (where p is 0 to 2; X is oxygen, sulfur or H_2)

where D and E can be attached to the B ring having the R^1 and R^2 substituents by either terminus of the linker;

each R^1 is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-C(O)OR^5$, $-C(O)N(R^5)R^6$, $-N(R^5)R^6$, $-O-C(O)R^5$, $-N(R^5)-CH(R^{12})-C(O)OR^5$, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$) or heterocyclylalkyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$);

R^2 is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, $-OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-C(O)OR^5$, $-C(O)N(R^5)R^6$, $-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-R^8-N(R^{10})R^{11}$, $-C(R^7)H-OR^5$, $-C(R^7)H-R^8-OR^5$, $-C(R^7)H-S(O)_p-R^9$ (where p is 0 to 2), $-C(R^7)H-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-O-R^8-S(O)_p-R^8$ (where p is 0 to 2), $-C(R^7)H-N(R^5)R^6$, $-C(R^7)H-R^8-N(R^5)R^6$, $-O-R^8-CH(OH)-CH_2-N(R^{10})R^{11}$, $-O-R^8-N(R^{10})R^{11}$, $-O-R^8-O-C(O)R^5$, $-O-R^8-CH(OH)-CH_2-OR^5$, $-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-(R^8-O)_t-R^{19}$ (where t is 1 to 6), $-O-R^8-C(O)R^5$, $-O-R^8-C(O)R^{19}$, $-O-R^8-C(O)OR^5$, $-N(R^5)-R^8-N(R^{10})R^{11}$, $-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2), $-S(O)_p-R^8-C(O)OR^5$ (where p is 0 to 2), or $-N(R^5)-CH(R^{12})-C(O)OR^5$;

R^3 is aryl or heterocyclyl both substituted by one or more R^{14} substituents independently selected from the group consisting of hydrogen, alkyl, halo, formyl, acetyl, cyano, $-R^8-CN$,

$-N(R^{10})R^{11}$, $-R^8-N(R^{10})R^{11}$, $-R^8-N^{\oplus}(R^9)(R^{16})_2$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-OR^5$, $-R^8-OR^5$,

$-C(R^7)H-O-R^{15}$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2),

$-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-(R^8-O)_t-R^5$

(where t is 1 to 6), $-R^8-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-R^8-O-(R^8-O)_t-R^5$ (where t is 1

to 6), $-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$.

-C(R⁷)H-N(R⁵)-R⁸-[CH(OH)]_t-CH₂-OR⁵ (where t is 1 to 6), -C(R⁷)H-N(R⁵)-S(O)₂-N(R¹⁰)R¹¹,
 -C(R⁷)H-N(R¹⁰)-C(NR¹⁷)-N(R¹⁰)R¹¹, -C(R⁷)H-N(R¹⁰)-C(NR¹⁷)-R¹⁰, -C(NR¹⁷)-N(R⁵)R⁶,
 -C(R⁷)H-C(NR¹⁷)-N(R⁵)R⁶, -C(R⁷)H-O-N(R⁵)R⁶, heterocyclyl (wherein the heterocyclyl
 radical is not attached to the rest of the molecule through a nitrogen atom and is optionally
 substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or
 -C(O)N(R⁵)R⁶), and heterocyclylalkyl (wherein the heterocyclyl radical is not attached to
 the alkyl radical through a nitrogen ring and is optionally substituted by one or more
 substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo,
 -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

each R⁴ is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶,
 -C(O)N(R⁵)R⁶, or -R⁸-N(R⁵)R⁶;

each R⁵ and R⁶ is independently hydrogen, alkyl, aryl or aralkyl;

each R⁷ is independently hydrogen or alkyl;

each R⁸ is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R⁹ is independently alkyl, aryl or aralkyl;

each R¹⁰ and R¹¹ is independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, -R⁸-CN,
 -OR⁵, -R⁸-OR⁵, -S(O)_p-R¹⁵ (where p is 0 to 2), -R⁸-S(O)_p-R¹⁵ (where p is 0 to 2), -N(R⁵)R⁶,
 -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, -C(O)-R¹⁵, -C(O)NH₂, -R⁸-C(O)NH₂, -C(S)NH₂, -C(O)-S-R⁵,
 -C(O)-N(R⁵)R¹⁵, -R⁸-C(O)-N(R⁵)R¹⁵, -C(S)-N(R⁵)R¹⁵, -R⁸-N(R⁵)-C(O)H, -R⁸-N(R⁵)-C(O)R¹⁵,
 -C(O)O-R⁸-N(R⁵)R⁶, -C(N(R⁵)R⁶)=C(R¹⁶)R¹⁰, -R⁸-N(R⁵)-P(O)(OR⁵)₂, cycloalkyl (optionally
 substituted by one or more substituents selected from the group consisting of alkyl, halo
 and -OR⁵), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo,
 -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2),
 -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more
 substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo,
 -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is 0 to 2),
 -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

or R¹⁰ and R¹¹ together with the nitrogen to which they are attached form a *N*-heterocyclic ring
 containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally
 substituted by one or more substituents selected from the group consisting of alkyl, halo,
 haloalkyl, aryl, aralkyl, oxo, nitro, cyano, -R⁸-CN, =N(R¹⁷), -OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵,
 -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -C(O)N(R⁵)R⁶, -R⁸-C(O)N(R⁵)R⁶, -N(R⁵)-N(R⁵)R⁶, -C(O)R⁵,
 -C(O)-(R⁸-O)_t-R⁵ (where t is 1 to 6), -S(O)_p-R⁹ (where p is 0 to 2), -R⁸-S(O)_p-R⁹ (where p is
 0 to 2), -(R⁸-O)_t-R⁵ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or
 more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl,

$-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$, and $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$;

R^{12} is a side chain of an α -amino acid;

each R^{15} is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, $-\text{R}^8-\text{O}-\text{C}(\text{O})-\text{R}^5$, $-\text{R}^8-\text{OR}^5$,

$-\text{N}(\text{R}^5)\text{R}^6$, $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$, $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{R}^8-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$, and $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{R}^8-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$, and $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$);

or R^5 and R^{15} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, OR^5 , $-\text{C}(\text{O})\text{OR}^5$, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R^{16} is independently alkyl, aryl, aralkyl, $-\text{R}^8-\text{OR}^5$, $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-\text{OR}^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ or $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ and $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$); or

both R^{16} 's together with the nitrogen to which they are attached (and wherein the R^9 substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, $-\text{OR}^5$, $-\text{R}^8-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$, $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$, $-\text{C}(\text{O})\text{R}^5$, $-\text{C}(\text{O})-(\text{R}^8-\text{O})_t-\text{R}^5$ (where t is 1 to 6), and $-(\text{R}^8-\text{O})_t-\text{R}^5$ (where t is 1 to 6);

each R^{17} is independently hydrogen, alkyl, aryl, aralkyl, cyano, $-\text{OR}^5$, $-\text{R}^8-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$, $-\text{C}(\text{O})-\text{N}(\text{R}^5)\text{R}^6$, or $-\text{R}^8-\text{C}(\text{O})-\text{N}(\text{R}^5)\text{R}^6$;

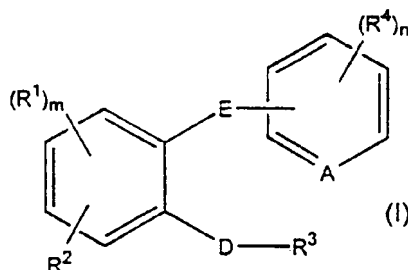
R^{18} is hydrogen, alkyl, aryl, aralkyl, cyano, $-\text{C}(\text{O})\text{OR}^5$, or $-\text{NO}_2$; and

each R^{19} is cycloalkyl, haloalkyl, $-\text{R}^8-\text{OR}^5$, $-\text{R}^8-\text{N}(\text{R}^5)\text{R}^6$, $-\text{R}^8-\text{C}(\text{O})\text{OR}^5$, $-\text{R}^8-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ or $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, $-\text{OR}^5$, $-\text{C}(\text{O})\text{OR}^5$, $-\text{N}(\text{R}^5)\text{R}^6$ and $-\text{C}(\text{O})\text{N}(\text{R}^5)\text{R}^6$);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof;

for the production of a medicament for the treatment of a human having a disease-state characterized by thrombotic activity.

69. Use of Claim 68, of a therapeutically effective amount of a compound of formula (I):



A is =CH- or =N-;

m is 1 to 3;

n is 1 to 4;

D is -N(R⁵)-C(Z)- or -N(R⁵)-S(O)_p- (where p is 0 to 2; Z is oxygen, sulfur or H₂; and the nitrogen atom is directly bonded to the phenyl ring having the R¹ and R² substituents);

E is -C(Z)-N(R⁵)- or -S(O)_p-N(R⁵)- (where p is 0 to 2; Z is oxygen, sulfur or H₂; and the nitrogen atom can be bonded to the phenyl ring having the R¹ and the R² substituents or to the aromatic ring having the R⁴ substituent);

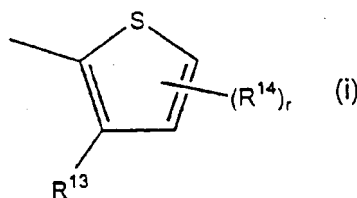
each R¹ is independently hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -C(O)OR⁵, -C(O)N(R⁵)R⁶, -N(R⁵)R⁶, -O-C(O)R⁵, or -N(R⁵)-CH(R¹²)-C(O)OR⁵;

or two adjacent R¹'s together with the carbons to which they are attached form a heterocyclic ring fused to the phenyl ring wherein the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl and aralkyl;

R² is hydrogen, alkyl, aryl, aralkyl, halo, haloalkyl, cyano, -OR⁵, -S(O)_p-R⁹ (where p is 0 to 2), -C(O)OR⁵, -C(O)N(R⁵)R⁶, -N(R¹⁰)R¹¹, -C(R⁷)H-N(R¹⁰)R¹¹, -C(R⁷)H-R⁸-N(R¹⁰)R¹¹, -C(R⁷)H-OR⁵, -C(R⁷)H-R⁸-OR⁵, -C(R⁷)H-S(O)_p-R⁹ (where p is 0 to 2), -C(R⁷)H-R⁸-S(O)_p-R⁹ (where p is 0 to 2), -O-R⁸-S(O)_p-R⁹ (where p is 0 to 2), -C(R⁷)H-N(R⁵)R⁶, -C(R⁷)H-R⁸-N(R⁵)R⁶, -O-R⁸-CH(OH)-CH₂-N(R¹⁰)R¹¹, -O-R⁸-N(R¹⁰)R¹¹, -O-R⁸-O-C(O)R⁵, -O-R⁸-CH(OH)-CH₂-OR⁵, -O-(R⁸-O)_t-R⁵ (where t is 1 to 6), -O-(R⁸-O)_t-R¹⁹ (where t is 1 to 6), -O-R⁸-C(O)R⁵, -O-R⁸-C(O)R¹⁹, -O-R⁸-C(O)OR⁵, -N(R⁵)-R⁸-N(R¹⁰)R¹¹, -S(O)_p-R⁸-N(R⁵)R⁶ (where p is 0 to 2), -S(O)_p-R⁸-C(O)OR⁵ (where p is 0 to 2), or -N(R⁵)-CH(R¹²)-C(O)OR⁵;

R³ is a radical of formula (I):

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where:

r is 1 or 2;

R^{13} is hydrogen, alkyl, halo, haloalkyl, $-N(R^5)R^6$, $-C(R^7)H-N(R^5)R^6$, $-OR^5$, $-R^8-OR^5$,

$-S(O)_p-R^8-N(R^5)R^6$ (where p is 0 to 2) or heterocyclalkyl (where the heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, aralkyl, nitro and cyano); and

each R^{14} is independently hydrogen, alkyl, halo, formyl, acetyl, cyano, $-R^8-CN$, $-N(R^{10})R^{11}$,

$-C(R^7)H-N(R^{10})R^{11}$, $-C(R^7)H-R^8-N(R^{10})R^{11}$, $-C(R^7)H-N^+(R^9)(R^{16})_2$,

$-C(R^7)H-R^8-N^+(R^9)(R^{16})_2$, $-C(O)OR^5$, $-C(R^7)H-C(O)OR^5$, $-C(R^7)H-R^8-C(O)OR^5$,

$-OR^5$, $-C(R^7)H-OR^5$, $-C(R^7)H-R^8-OR^5$, $-C(R^7)H-O-R^{15}$, $-S(O)_p-R^{15}$ (where p is 0 to

2), $-C(R^7)H-S(O)_p-R^{15}$ (where p is 0 to 2), $-C(R^7)H-R^8-S(O)_p-R^{15}$ (where p is 0 to 2),

$-S(O)_p-N(R^5)R^6$ (where p is 0 to 2), $-C(O)N(R^5)R^6$, $-C(R^7)H-C(O)N(R^5)R^6$,

$-C(R^7)H-R^8-C(O)N(R^5)R^6$, $-C(R^7)H-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6),

$-C(R^7)H-R^8-N(R^5)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-C(R^7)H-O-(R^8-O)_t-R^5$ (where t is 1

to 6), $-C(R^7)H-R^8-O-(R^8-O)_t-R^5$ (where t is 1 to 6), $-O-R^8-CH(OH)-CH_2-OR^5$,

$-C(R^7)H-O-R^8-CH(OH)-CH_2-OR^5$, $-C(R^7)H-N(R^5)-R^8-[CH(OH)]_t-CH_2-OR^5$ (where t is

1 to 6), $-C(R^7)H-N(R^5)-S(O)_2-N(R^{10})R^{11}$, $-C(R^7)H-N(R^{10})-C(NR^{17})-N(R^{10})R^{11}$,

$-C(R^7)H-N(R^{10})-C(NR^{17})-R^{10}$, $-C(NR^{17})-N(R^5)R^6$, $-C(R^7)H-C(NR^{17})-N(R^5)R^6$,

$-C(R^7)H-O-N(R^5)R^6$, heterocyclyl (wherein the heterocyclyl radical is not attached

to the radical of formula (i) through a nitrogen atom and is optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ or

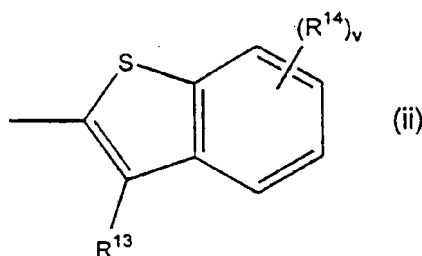
$-C(O)N(R^5)R^6$), or heterocyclalkyl (wherein the heterocyclalkyl radical is not

attached to the alkyl radical through a nitrogen atom and is optionally substituted

by one or more substituents selected from the group consisting of alkyl, aryl,

aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$;

or R^3 is a radical of the formula (ii):



where v is 1 to 4;

R^{13} is as defined above for formula (i); and

R^{14} is as defined above for formula (i);

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, cyano, nitro, $-OR^5$, $-C(O)OR^5$, $-N(R^5)R^6$, $-C(O)N(R^5)R^6$, or $-R^8-N(R^5)R^6$;

R^5 and R^6 are each independently hydrogen, alkyl, aryl or aralkyl;

each R^7 is independently hydrogen or alkyl;

each R^8 is independently a straight or branched alkylene, alkylidene or alkylidyne chain;

each R^9 is independently alkyl, aryl or aralkyl;

R^{10} and R^{11} are each independently hydrogen, alkyl, haloalkyl, aryl, aralkyl, formyl, cyano, $-R^8-CN$, $-OR^5$, $-R^8-OR^5$, $-S(O)_p-R^{15}$ (where p is 0 to 2), $-R^8-S(O)_p-R^{15}$ (where p is 0 to 2), $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-R^8-C(O)OR^5$, $-C(O)-R^{15}$, $-C(O)NH_2$, $-R^8-C(O)NH_2$, $-C(S)NH_2$, $-C(O)-S-R^5$, $-C(O)-N(R^5)R^{15}$, $-R^8-C(O)-N(R^5)R^{15}$, $-C(S)-N(R^5)R^{15}$, $-R^8-N(R^5)-C(O)H$, $-R^8-N(R^5)-C(O)R^{15}$, $-C(O)O-R^8-N(R^5)R^6$, $-C(N(R^5)R^6)=C(R^{18})R^{10}$, $-R^8-N(R^5)-P(O)(OR^5)_2$, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and $-OR^5$), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ or $-C(O)N(R^5)R^6$), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, oxo, $-OR^5$, $-R^8-OR^5$, $-C(O)OR^5$, $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-N(R^5)R^6$ and $-C(O)N(R^5)R^6$);

or R^{10} and R^{11} together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, haloalkyl, aryl, aralkyl, oxo, nitro, cyano, $-R^8-CN$, $=N(R^{17})$, $-OR^5$, $-C(O)OR^5$, $-R^8-C(O)OR^5$, $-N(R^5)R^6$, $-R^8-N(R^5)R^6$, $-C(O)N(R^5)R^6$, $-R^8-C(O)N(R^5)R^6$, $-N(R^5)-N(R^5)R^6$, $-C(O)R^5$, $-C(O)-(R^8-O)_t-R^5$ (where t is 1 to 6), $-S(O)_p-R^9$ (where p is 0 to 2), $-R^8-S(O)_p-R^9$ (where p is 0 to 2), $-(R^8-O)_t-R^5$ (where t is 1 to 6), and heterocyclyl (optionally substituted by one or

more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶;

R¹² is a side chain of an α -amino acid;

each R¹⁵ is independently alkyl, cycloalkyl, haloalkyl, aryl, aralkyl, -R⁸-O-C(O)-R⁵, -R⁸-OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, heterocyclyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -N(R⁵)R⁶, and -C(O)N(R⁵)R⁶);

or R⁵ and R¹⁵ together with the nitrogen to which they are attached form a *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, -OR⁵, -C(O)OR⁵, aminocarbonyl, monoalkylaminocarbonyl, and dialkylaminocarbonyl;

each R¹⁶ is independently alkyl, aryl, aralkyl, -R⁸-OR⁵, -R⁸-N(R⁵)R⁶, cycloalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, halo and -OR⁵), heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶); or

both R¹⁶'s together with the nitrogen to which they are attached (and wherein the R⁹ substituent is not present) form an aromatic *N*-heterocyclic ring containing zero to three additional hetero atoms, where the *N*-heterocyclic ring is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, -OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -N(R⁵)R⁶, -R⁸-N(R⁵)R⁶, -C(O)R⁵, -C(O)-(R⁸-O)_t-R⁵ (where *t* is 1 to 6), and -(R⁸-O)_t-R⁵ (where *t* is 1 to 6);

each R¹⁷ is independently hydrogen, alkyl, aryl, aralkyl, cyano, -OR⁵, -R⁸-OR⁵, -C(O)OR⁵, -R⁸-C(O)OR⁵, -C(O)-N(R⁵)R⁶, or -R⁸-C(O)-N(R⁵)R⁶;

R¹⁸ is hydrogen, alkyl, aryl, aralkyl, cyano, -C(O)OR⁵, or -NO₂; and

each R¹⁹ is cycloalkyl, haloalkyl, -R⁸-OR⁵, -R⁸-N(R⁵)R⁶, -R⁸-C(O)OR⁵, -R⁸-C(O)N(R⁵)R⁶, heterocyclyl (optionally substituted by alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ or -C(O)N(R⁵)R⁶), or heterocyclylalkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, -OR⁵, -C(O)OR⁵, -N(R⁵)R⁶ and -C(O)N(R⁵)R⁶);

as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof, for the production of a medicament for the treatment of a human having a disease-state characterized by thrombotic activity.